

## **The HDE Summary of Safety and Probable Benefit What It Is and Does**

Under section 520(m) of the Federal Food, Drug, and Cosmetic Act (FD&C), the Secretary may approve a Humanitarian Device Exemption (HDE) application, which exempts the device from the effectiveness requirements of sections 514 and 515. Although the device is exempt from demonstrating effectiveness, there must be sufficient information to show a probable benefit for its intended use and indication for use. The Summary of Safety and Probable Benefit (SSPB) is an FDA document (originally submitted by the applicant and modified by FDA) which is intended to present a reasoned, objective, and balanced critique of the scientific evidence which served as the basis for the approval of the HDE. The SSPB documents that there is reasonable assurance of safety and probable benefit for the device as labeled based on the nonclinical and clinical information described in the HDE. The SSPB is a summation of both the positive and negative aspects of the scientific evidence. For a HDE to be approved, the potential risks versus possible benefits assessment must favor this action in conjunction with a comparison to all the possible alternatives. The SSPB summarizes these judgements.

The SSPB is a publicly releasable document, which the applicant is required to submit under 21 CFR 814.104(b)(4). The applicant's SSPB often differs from FDA's objective, i.e., it contains only the positive aspects of the device; it contains marketing language, etc. Consequently, revision is often needed. Since minor variations in SSPB formats are possible, it is best to consult previously released SSPBs (preferably recent ones for similar devices) for guidance and to consult with the HDE staff. Since the SSPB deals with scientific/technical data and will be read by many non-professionals, it is best to keep the format clear by grouping study objective(s), study methods, results, interpretation(s), and conclusion(s) for each study or substudy. An overall statement/conclusion integrating the individual study outcomes in light of safety and probable benefit should be written. The SSPB should be as concise as possible.

Note: In creating this template, parts of the *General Program Memorandum #G91-1: Device Labeling Guidance* was incorporated. This guidance can be referenced at the following web page: <http://www.fda.gov/cdrh/g91-1.html>

## SUMMARY OF SAFETY AND PROBABLE BENEFIT

### I. GENERAL INFORMATION

Device Generic Name:	Implantable retinal prosthesis
Device Trade Name:	Argus® II Retinal Prosthesis System
Applicant's Name & Address:	Second Sight Medical Products, Inc. 12744 San Fernando Road, Building 3 Sylmar, CA 91342
Humanitarian Device Exemption (HDE) Number:	H110002
Humanitarian Use Device (HUD) Designation Number:	#09-0216
Date of Humanitarian Use Device (HUD) Designation:	May 28, 2009
Date(s) of Panel Recommendation:	September 29, 2012
Date of Good Manufacturing Practice Inspection:	October 18, 2011
Date of Notice of Approval to Applicant:	February 13, 2013

### II. INDICATIONS FOR USE

The Argus II Retinal Prosthesis System is intended to provide electrical stimulation of the retina to induce visual perception in blind patients. It is indicated for use in patients with severe to profound retinitis pigmentosa who meet the following criteria:

- Adults, age 25 years or older.
- Bare light or no light perception in both eyes. (If the patient has no residual light perception, then evidence of intact inner layer retina function must be confirmed.)
- Previous history of useful form vision.
- Aphakic or pseudophakic. (If the patient is phakic prior to implant, the natural lens will be removed during the implant procedure.)
- Patients who are willing and able to receive the recommended post-implant clinical follow-up, device fitting, and visual rehabilitation<sup>1</sup>.

The Argus II implant is intended to be implanted in a single eye, typically the worse-seeing eye.

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<sup>1</sup> The indication for use statement has been modified from that granted for the HUD designation request #09-0216. The HUD designation states that the device is indicated "to provide electrical stimulation of the retina to elicit visual perception in blind subjects with severe to profound retinitis pigmentosa." The current IFU further clarifies the intended population.

### III. CONTRAINDICATIONS

- Ocular diseases or conditions that could prevent the Argus II System from working (e.g. optic nerve disease, central retinal artery or vein occlusion, history of retinal detachment, trauma, severe strabismus, etc.). Ocular structures or conditions that could prevent the successful implantation of the Argus II Implant or adequate healing from surgery (e.g. extremely thin conjunctiva, axial length <20.5 mm or >26 mm, corneal ulcers, etc.).
- Ocular diseases or conditions (other than cataracts) that prevent adequate visualization of the inner structures of the eye (e.g. corneal opacity, etc.).
- Inability to tolerate general anesthesia or the recommended antibiotic and steroid regimen associated with the implantation surgery.
- Metallic or active implantable device(s) (e.g. cochlear implant) in the head.
- Any disease or condition (e.g. significant cognitive decline, etc.) that prevents understanding or communication of informed consent, fitting of the Argus II System, or post-operative follow-up. A pre-operative psychological evaluation may be recommended to confirm the patient is not contraindicated based on this criterion.
- Predisposition to eye rubbing.
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### IV. WARNINGS AND PRECAUTIONS

#### WARNINGS:

- **Failure to follow the recommended surgical procedure** for implanting the Argus II Implant may increase the risk of adverse events and damage to the implant.
- **Individuals implanted with an Argus II Implant should not undergo short wave or microwave diathermy.** High currents induced in the implant electrodes can cause tissue damage or serious injury. Diathermy may also cause permanent damage to the implant.
- **Individuals implanted with an Argus II Implant should not undergo electroconvulsive therapy (ECT)** as ECT may cause tissue damage or permanent damage to the implant.
- **If lithotripsy or high output ultrasound** must be used, do not focus the treatment beam near the Argus II Implant. Exposure of the Argus II Implant to these therapies may harm the patient or damage the implant.
- The Argus II Implant has been classified as an **MR Conditional** device. Individuals with an Argus II Implant may undergo a **magnetic resonance imaging (MRI)** procedure ONLY if it is performed using a 1.5 or 3.0 Tesla MRI

System and ONLY following the MRI Instructions provided later in this insert. Individuals with an Argus II Implant should not enter a room housing an MRI System that has a rating other than 1.5 or 3.0 Tesla, even if the Argus II System is not being used. The external equipment (i.e. VPU and glasses) should remain outside the MR system room, as **severe harm to people in the MR system room could occur**. If any pain is experienced during the MRI procedure the patient should be instructed to notify the technician immediately.

- The Argus II System may interfere with the operation or accuracy of **medical monitoring, diagnostic or life support equipment**. Do not use the Argus II System within 3 feet (0.9 meters) of this type of equipment. If interference occurs, turn off the Argus II VPU or extend the distance between yourself and the affected equipment.
- Do not use **monopolar electrosurgical equipment** in individuals with an Argus II Implant. Monopolar electrosurgical equipment may cause damage to the implant or to tissue surrounding the implant.

## PRECAUTIONS

- In the event of any **undesirable sensation** when using the Argus II System (for example, pain), immediately halt operation of the system by removing the Argus II Glasses or turning off the Argus II VPU.
- At any time after implantation, Argus II patients have a risk of conjunctival complications which, if left untreated, may result in conjunctival erosion which could lead to endophthalmitis. Argus II recipients should be vigilant in reporting any new symptoms of foreign body sensations, tearing and/or pain promptly to their eye care professional. Long-term professional monitoring for late conjunctival issues is necessary.
- The long-term effects of **chronic electrical stimulation** are unknown. Such effects may include deterioration of the retina or optic nerve. These effects may lead to deterioration of residual native vision and/or visual response to the Argus II System and could preclude subsequent replacement of the Argus II Implant with another retinal implant.
- Individuals with an Argus II Implant should **only use a VPU that has been specifically programmed for them** by their clinician or Second Sight personnel. Use of a different VPU may be ineffective in providing visual information and may cause physical discomfort from overstimulation.
- To avoid unsafe stimulation, do not use a **VPU configured for Operating Room** use for anything other than pre-implantation testing, testing during implantation, or initial fitting testing.
- Individuals with an Argus II Implant should **avoid physical impact or extreme direct pressure to the eye** as this may result in eye trauma, movement or damage to the Argus II Implant. If this occurs, consult your physician.
- Individuals with an Argus II Implant should **avoid eye rubbing** as this may dislodge the implant or cause eye irritation.

- Individuals with an Argus II Implant should continue to use their other **mobility aids** (e.g. canes, dogs, etc.) at all times.
- Use of the Argus II System during **pregnancy and nursing** has not been evaluated.

## PRECAUTIONS REGARDING OTHER MEDICAL PROCEDURES

### A. GENERAL INFORMATION (APPLICABLE TO ALL PROCEDURES):

- Individuals needing to undergo any of the procedures listed below, should inform his or her doctor about the existence of a retinal prosthesis in the eye. The doctor should contact Second Sight at 1-818-833-5060 for more information.
- **Before having any medical or test procedure that involves the use of other medical equipment, individuals with an Argus II Implant should remove the Argus II Glasses and VPU.**
- Once the procedure is complete, that individual should have the Argus II Implant tested as soon as possible to make sure it is still functioning properly. Damage to the implant may not be immediately detectable.

### B. INFORMATION ABOUT SPECIFIC PROCEDURES:

- **Magnetic Resonance Imaging (MRI)** – Refer to the Warnings section above
- The use of **laser, phacoemulsification, or fragmatome** may damage the Argus II Implant. If these procedures must be used in an implanted eye, do not direct the laser beam at the implant. Extra caution should be used when performing these procedures intraocularly as visualization of the implant may be obscured.
- The use of **bipolar electrosurgical equipment** may damage the Argus II Implant. Use caution when using this equipment near the implant.
- **CT Scans or Diagnostic Ultrasound** may be performed in individuals with an Argus II Implant. However, if a scan or ultrasound is performed in the region where the Argus II Implant is located, the implant may create an image artifact making the scan unreadable in this region.
- Use of **defibrillators or therapeutic ionizing radiation to the head** may permanently damage the Argus II Implant. However, this should not preclude or change the way in which these treatments are delivered. The Argus II Implant should be tested by a qualified clinician or Second Sight personnel as soon as possible following the procedure or defibrillator activation to confirm that it is still functioning properly. Damage to the implant may not be immediately detectable.

- The effects of cobalt treatment and linear acceleration techniques on the implant are unknown.

### **C. ELECTROMAGNETIC INTERFERENCE (EMI):**

Electromagnetic interference is a field of energy (electrical, magnetic, or both) created by equipment found in public environments that may be strong enough to interfere with the normal operation of the Argus II System. The Argus II System meets international standards for electromagnetic compatibility and is designed to continue to operate in a “safe mode” in the presence of any electromagnetic interference which would normally be encountered during every day use of the Argus II System. It is important to note, however, that in certain circumstances, electromagnetic interference could cause the following:

- **Serious injury.** Exposure of the implant to EMI may result in the implant heating and damaging nearby retinal tissue.
- **Damage to the Argus II implant.** Damage to the implant may require replacement, or result in loss of, or irreversible change in the performance of the Argus II System.
- **Unexpected Turning off of the Argus II VPU.** EMI may cause the VPU to turn off unexpectedly.
- **Interruption of Stimulation.** EMI may cause a momentary interruption of stimulation.

Argus II System users should be advised that upon entering an environment which maybe causing interference with the Argus II System, they should move away from the equipment or object thought to be causing the interference, if possible, turn off the equipment or object causing the interference, tell the equipment operator or the doctor what happened and, if they continue to experience interference or think that the Argus II System is not working as well as it did before they encountered the interference, to contact their doctor.

### **D. POSSIBLE INTERFERENCE WITH OTHER ELECTRONIC DEVICES**

- **Theft or metal detectors** (such as those located in entrances to public buildings and department stores) and airport or security screening devices may temporarily interrupt Argus II stimulation if the Argus II System is used within 1 yard (0.9 meters) of them. Normal operation will resume when you move away from these items. When possible, it is best to avoid these devices or turn the VPU off when

passing through these systems. Individuals with an Argus II Implant should show their ID card to any attendant in the area who may be able to assist them in bypassing the devices. If unavoidable, walk through the scanner and promptly move away from the area. Do not lean on these scanners or linger in their path.

- **Electronic Article Surveillance (EAS) systems, EAS Tag Deactivators, and Radiofrequency identification (RFID) systems** may temporarily interrupt Argus II stimulation if the Argus II System is used within 3.5 yards (3.2 meters) of them. Normal operation will resume when you move away from these items. RFID systems and EAS systems and tag deactivators send out energy fields that wirelessly communicate with tags that are attached to objects such as merchandise, materials and people. These systems are used for security, theft prevention, tracking and inventory control and they are usually found in retail stores, libraries, government buildings, warehouses and offices. For example, security tags attached to clothing contain RFID tags.
- **Electrostatic Discharge (ESD)** may interfere with normal operation or cause damage to the electrical components of the Argus II System. Common situations that create static electricity include putting on or removing clothes, or dragging feet across a carpet or rug when there is less than 30% relative humidity. Care should be taken to avoid handling the VPU and glasses when static electricity is present.
- The Argus II System may interfere with the normal operation of some models of **hearing aids**. Hearing aids should be tested prior to implantation, to ensure proper functioning of both the Argus II System and the hearing device.
- Some **home appliances** (for example, microwaves ) and some **devices with antennae** (for example, cell phones, and cordless phones) may temporarily interrupt Argus II stimulation if the Argus II System is being used near them. The table below lists the distance at which interruption of stimulation may occur with these systems.

**Table 1: Separation Distances**

<b>Type of device</b>	<b>Interruption of stimulation may occur if device is operated within this distance of the Argus II System</b>
Another Argus II System	7 inches (17.5 cm)
Cell phone	1 inch (2.5 cm)
Cordless phone	1 inch (2.5 cm)
Bluetooth device	1 inch (2.5 cm)
Microwave oven	1 inch (2.5 cm)

WiFi Access Point	8 inches (20 cm)
Wireless Router	8 inches (20 cm)

Normal operation will resume when you move away from these items.

- The Argus II System operates using wireless technology which could interfere with the safe operation of an **airplane**. Patients should not turn on the Argus II System on an airplane.
- **Commercial electrical equipment** (such as arc welders, induction furnaces or resistance welders), **communication equipment** (such as microwave transmitters, linear power amplifiers and high-power amateur transmitters), **high voltage lines, power lines or generators, electric steel furnaces, or large magnetized speakers** may temporarily interrupt Argus II System function. Normal operation will resume when you move away from these items.

Additional information on specific environments and recommended separation distances is provided in the Electromagnetic Environments section of the Product Insert.

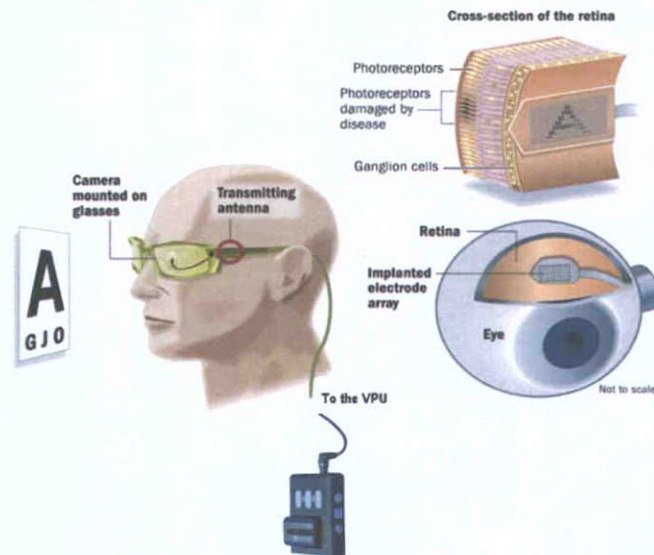
## V. DEVICE DESCRIPTION

The Argus II System is composed of three subsystems: The retinal prosthesis (implant), the Externals System and the Fitting System. The implant works in unison with the Externals System to deliver electrical stimulation to the retina. The third subsystem (Fitting System) is used in conjunction with the implant and Externals System in the clinic when fitting the device to the patient.

### PRINCIPLE OF OPERATION

The principle of operation of the Argus II System is shown schematically in Figure 1.





**FIGURE 1: SCHEMATIC OVERVIEW OF THE ARGUS II SYSTEM**

A video camera that is attached to glasses worn by the patient captures a video image. The camera signal is sent to a Video Processing Unit (VPU), worn by the patient on a belt or strap, which processes the camera image and transforms it into electrical stimulation patterns. The electrical stimulation data are then sent to a receiving/transmitter coil mounted on the glasses which sends both data and power wirelessly via radio-frequency (RF) telemetry to the implanted retinal prosthesis. The implant receives the radio-frequency commands and delivers stimulation to the retina via a thin film electrode array that is secured to the retina with a retinal tack. The pulses are intended to mimic the function of photoreceptor cells (which have lost most, if not all, of their functionality in this patient population) by inducing cellular responses in the remaining neurons that travel through the optic nerve to the visual cortex, where they are perceived as phosphenes of light.

A fitting process is periodically performed with the patient in the clinic to develop the stimulation parameters used to process the video images from the camera. This is accomplished through use of the Clinician Fitting System (CFS) which consists of fitting software with a graphical user interface running on a laptop computer. The patient specific configuration files developed from the fitting process are downloaded to the VPU where they are available for use by the patient.

A description of each of the subsystems follows.

## **IMPLANT SUBSYSTEM**

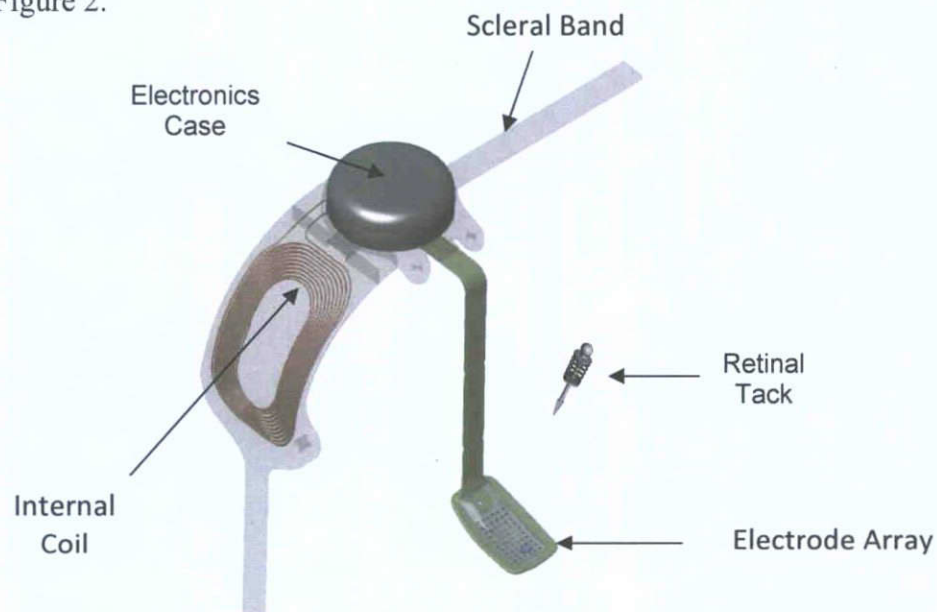
This subsystem is composed of the Argus II Retinal Prosthesis and the Argus II Retinal Tack. Each is described below.

## RETINAL PROSTHESIS

The retinal prosthesis, which is implanted in and on the eye and electrically stimulates the retina, consists of the following four major components:

- A small hermetic package that contains the electronics to receive power and to drive the electrical stimulation of the electrodes. A suture tab assembly encircles the package.
- A coil that receives power and receives and transmits data to/from the external primary coil (on the glasses).
- A thin film electrode cable and array that is electrically connected to the package and transmits the stimulation signals to the retina via 60 exposed platinum electrodes which are arranged in a  $6 \times 10$  pattern. The electrode array is secured to the retina with a retinal tack. The implant has 55 of these electrodes enabled for use.
- A scleral band that allows the implant to be secured to the outside of the eye.

An illustration of the Argus II Retinal Prosthesis showing each of its components is provided in Figure 2.



**FIGURE 2: ARGUS II RETINAL PROSTHESIS**

The Argus II Retinal Prosthesis is intended to be implanted in just one eye, typically the worse-seeing eye. The retinal prosthesis is provided sterile.

## RETINAL TACKS

Two retinal tacks are included with the retinal prosthesis. Modeled after a standard retinal tack, which was once commonly used to repair retinal detachments, the Argus II Retinal Tack is used to affix the electrode array to the retina. A single tack is used to secure the array. The second tack acts as a back-up. The tack is constructed from a biocompatible

titanium alloy used in other commercially available retinal tacks. The retinal tack includes a sharply pointed end for piercing through the retina, choroid, and sclera, and an elongated, cylindrical shaft. The tack also includes an enlarged head and flange as well as a spring that applies a gentle compressive force to hold the array down. When securing the electrode array to the retina, the retinal tack is placed through a tack hole on the electrode array.

## **EXTERNALS SUBSYSTEM**

The Externals System is composed of the Argus II Glasses and the Argus II Video Processing Unit. Each is described below.

### **GLASSES**

The Argus II Glasses provide a convenient and discreet way to house the video camera for capturing images and the radio-frequency system needed to power and communicate with the implant.

A small, light-weight video camera is mounted in the center of the frame above the nose-piece. The telemetry coils and radio-frequency system are mounted on the ear piece. The position of the coil housing is adjustable to provide comfort to the patient and to allow the external coil assembly to be optimally positioned relative to the implant coil to achieve a good communication link for patients with different facial structures.

The Argus II OR coil, although used only during the implantation surgery, is categorized as part of the Externals System. It is comprised of the same telemetry coil and RF system used in the glasses. The OR coil is used to test functionality of the implant during surgical implantation. It is placed in a sterile sleeve in the operating room.

### **VIDEO PROCESSING UNIT (VPU)**

The Argus II VPU, which powers and controls the implant, is comprised of a case, buttons, connectors, rechargeable battery and digital circuit boards. The buttons are large and shaped so that they can be easily identified by touch. There is one connector that connects the VPU to the glasses that can be easily connected by a sightless person. The VPU can also be connected to the Argus II Clinical Fitting System to allow testing of the implant and programming of the VPU ("patient fitting").

The VPU acquires video input from the camera and converts it into a digital format. Filters, such as edge detection and contrast adjustment, may be then applied. The image is then reduced to a 6 x 10 resolution using a downscaling filter. This representation of the image is then mapped to stimulation intensity using customized look-up tables that have been derived during the patient fitting process. A check is performed to assure that the overall current and the maximum charge per phase are within safety limits. The stimulation parameters are then sent via telemetry to the implant.

Prior to use, the VPU is configured to the patient's implant utilizing the Argus II VPU-Implant Matching CD.

## **FITTING SUBSYSTEM**

The primary components comprising the fitting subsystem are the Argus II Clinician Fitting System (CFS), the Argus II Psychophysical Test System (PTS), and the Argus II Communication Adapter (CA). Supporting accessories include various cables, USB drives, user input device and touch screen monitor. The components are described below.

### **CLINICIAN FITTING SYSTEM (CFS)**

The CFS consists of dedicated fitting software with a graphical user interface running on a laptop computer. The CFS is used to perform diagnostic tests of the system (e.g., electrode impedance), measure patient response to stimulation (e.g., thresholds), and configure the system stimulation parameters and video processing strategies for each patient.

The CFS includes software modules that allow the clinician to quickly administer tests to measure important perceptual parameters, such as electrical stimulation threshold. Based on these perceptual parameters, the fitting software allows the clinician to custom configure the transformation between the video image and electrode stimulation parameters thereby optimizing the retinal prosthesis for each patient.

The patient-specific configuration files developed from the fitting process can be downloaded to the VPU where they are available for use by the patient. The stimulation parameters are checked by CFS (in addition to the VPU) to ensure that only safe stimulation is delivered.

The CFS laptop is provided with a power supply unit for recharging the PC battery and a cable for connecting the CFS laptop to the Communication Adapter. The CFS software and VPU firmware ensure that the stimulation delivered to the patient are within specified safety limits.

### **PSYCHOPHYSICAL TEST SYSTEM (PTS)**

The PTS is an optional system component that consists of a laptop with an application programming interface (API) that the clinician can utilize to run scripts (programs) for evaluating patient performance with the Argus II System. The PTS is connected to the CFS. The PTS laptop is provided with a power supply unit for recharging the PC battery and a cable for connecting the PTS laptop to the CFS laptop. The CFS software and VPU firmware ensure that the stimulation parameters of the PTS developed scripts are within specified safety limits.

## **COMMUNICATION ADAPTER (CA)**

The CA provides an optically isolated communication channel between the CFS and the VPU, thus preventing the flow of electric current between the CFS and VPU.

## **TOUCH SCREEN MONITOR**

The touch screen monitor is an off-the-shelf component that is used as a tool for fitting the patient and for performing psychophysical tests in the clinic. The monitor is supplied with a medical grade power supply.

## **OTHER ACCESSORIES**

Other accessories used during the fitting process include cables for connecting the Fitting System to Externals System (Argus II CA-VPU Cable, Argus II CFS-CA Cable, and the Argus II CFS-PTS Cable) and USB drives for obtaining access to the Fitting System and for collecting transferring, and archiving data (Argus II USB Security Drive, Argus II USB Video Settings Drive, Argus II USB Transfer Drive, Argus II Archive Drive). A video gamepad controller and touch screen monitor for collecting patient responses may also be employed in the clinic.

## **VI. ALTERNATIVE PRACTICES AND PROCEDURES**

There are no commercialized treatment options currently available for RP patients. Traditionally, the approach to vision rehabilitation in patients with RP has been to use the remaining vision with the assistance of optical aides. In patients with no remaining useful vision, tools to maximize auditory or tactile information (e.g. Braille, cane travel, etc.) are used.

## **VII. MARKETING HISTORY**

The Argus II System received approval for commercial distribution in the European Economic Area (EEA) on February 10, 2011. Second Sight began commercially distributing the device in Europe in October 2011. The device has not been marketed in the US.

The Argus II Retinal Prosthesis System has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

## **VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH**

The following potential device- or implant surgery- related adverse events were not observed during the clinical trial:

- Facial nerve stimulation, transient electrical shock, skin burn due to excessive heating of the external equipment, or retinal tissue damage due to mechanical trauma, excessive stimulation or excessive heating of the implant.
- Failure or damage to the Argus II Implant requiring it to be explanted.
- Fall or bump resulting from use of the Argus II System.
- Risks known to be associated with standard vitreo-retinal surgery, peeling of an epiretinal membrane and use of a scleral band: suprachoroidal hemorrhage, intrusion/extrusion of the scleral band, and macular hole.
- Risks known to be associated with the removal of the lens using clear cornea phacoemulsification: cortical drop in vitreous or vitreous prolapse.
- Risks known to be associated with canthotomy: improper apposition of the eyelids and chronic irritation at the lid margin.
- Risks known to be associated with the use of general anesthesia, steroids and antibiotics: chest pain, urinary retention, myocardial infarction, pulmonary embolism, deep vein thrombosis, respiratory failure, blood loss requiring transfusion, systemic infection, prolonged hospitalization, and allergic reaction to anesthesia.
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## **IX. SUMMARY OF PRECLINICAL STUDIES**

### **LABORATORY STUDIES**

Objectives: The objectives of the laboratory studies were to test performance, safety and reliability of the Argus II System. Testing was performed on a component level, sub-assembly level, device level and system level. Provided below is a summary of testing. Testing has been categorized by subsystems comprising the Argus II System.

### **SUMMARY OF LABORATORY STUDIES: IMPLANT**

A summary of the bench testing performed on the implant components, subassemblies, and the final device is provided in Table 2.

**TABLE 2: SUMMARY OF LABORATORY STUDIES FOR IMPLANT & IMPLANT COMPONENTS/SUB-ASSEMBLIES**

<b>Implant Component: Array</b>
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<b>Implant Component: Array</b>
<p><u>Flexure Fatigue Test</u>: Testing was performed to verify that the electrode array can withstand the flexure forces which might occur during or after implantation. The specification was developed with a margin of safety from normal stresses anticipated during actual use. Flexure fatigue testing was performed on samples soaked in saline. A determination was made of the number of flexure cycles until trace failure, as defined as loss of electrical continuity, was observed. The array was determined to meet specification.</p>
<p><u>Active Soak Test</u>: Testing was performed to verify that the electrode array meets its long-term electrical stimulation specification, i.e., that it permits stimulation at the maximum charge density limit at 30 Hz (baseline frequency) for the equivalent of 5 years in saline. Test samples were exposed to accelerated aging conditions. Arrays stimulating at accelerated active stimulation reached the equivalent of 32 years of real-time use with no significant changes in voltage waveform.</p>
<p><u>Stimulation Test</u>: Testing was performed to verify that the array satisfies its electrical specifications for insulation resistance, capacitance between traces, and electrode series resistance and capacitance. Specification was based on the requirement that current levels be isolated so as not to induce percepts on adjacent channels. Testing was performed in the presence of saline. The array was determined to meet specification.</p>
<p><u>Mechanical Test</u>: Testing was performed to verify that the electrode array continues to meet its specification for shape and curvature after exposure to expected thermal excursions, sterilization, and the forces of surgical implantation. s.</p>
<b>Implant Component: Coil</b>
<p><u>Flexure / Soak Test</u>: Testing was performed to verify that the coil meets its electrical specifications (inductance, quality factor, and self resonance frequency) after being exposed to the forces which might occur during or after implantation. Implant coils were tested under accelerated aging conditions under a maximum electrical load. Coils were subjected to a flexure test to introduce mechanical stress on the coils prior to lifetime soak test. The coil was determined to meet its specified tolerances.</p>
<p><u>Mechanical Test</u>: Tear strength testing was performed to verify that the coil suture tab could withstand the tear forces incurred during implantation of the device. The suture tabs met acceptance criteria.</p>
<b>Implant Component: Application Specific Integrated Circuit (ASIC)</b>
<p><u>Performance Test</u>: Testing was performed on the retina chip (i.e., ASIC) to verify that it meets defined specifications for (1) Power supply and reset characteristics (2) Receiver characteristics (3) Electrode driver output characteristics (4) System control characteristics (5) Back telemetry characteristics and (6) Test interface. The ASIC met specifications.</p>

**Implant Sub-assembly: Package**

Corrosion Test: Samples of the package were subjected to active and passive soaking to study corrosion effects on the package's lifetime. Testing included EDX/SEM analysis and electrochemical impedance spectroscopy (EIS) measurements of the hardcase. No evidence of any corrosion including galvanic corrosion occurred on native metal of the cases. Moreover, no change in impedance of the hardcase, which serves as a return electrode, was detected.

Environmental Testing: Hermetically sealed packages were subject to temperature extremes, random vibration, and variations in atmospheric pressure to evaluate reliability of the implant to withstand the forces which may occur under normal conditions of storage, shipment and use. The hermetically sealed package of the implant met established acceptance criteria for temperature cycling, random vibration, internal water vapor content, and atmospheric pressure variation.

Mechanical Test / Design Analysis: A design analysis with tear strength testing was performed to verify that the suture tabs surrounding the hardcase could withstand the tear forces incurred during implantation of the device. The suture tabs met acceptance criteria.

**Implant (Assembled)**

Soak Test: Test samples equivalent to the actual device interconnect were evaluated to verify that the flex interconnection of the array, coil and package meets the design lifetime specification of at least 5 years in vitro under active soak conditions with a maximum electrical load. Testing was performed under accelerated aging conditions. The interconnect met its design lifetime specification.

Design Analysis: In addition to the above interconnect subassembly soak test, a design analysis was performed to assess the integrity of the coil attachment and the electrode array interconnect to withstand flexural stresses. The flexure forces were determined to be controlled by the design.

Environmental Testing: Packaged implants were subjected to random vibration, different atmospheric pressures, and temperature cycling (55° C and -10° C) to verify that the device can withstand the forces which may occur under normal conditions of shipping and use. Devices exposed to environmental testing continued to meet specifications for electrical functionality and visual integrity.

Diagnostic Ultrasound: Implants were evaluated for their compatibility to ultrasound exposure per EN 45502-1:1997. Devices exposed to ultrasound energy were able to power up with no change in the power characteristics. The safety checks that the implant performs on start-up were also unaffected.



<b>Implant (Assembled)</b>
<p><u>Diagnostic MRI:</u> Implants were evaluated for their compatibility to magnetic resonance imaging (MRI) per EN 45502-1:1997. Testing demonstrated that the implant and retinal tack are “MR Conditional” in 1.5 Tesla/64MHz and 3.0 Tesla/128 MHz MR environments.</p>
<p><u>Particulate Testing:</u> Implants were tested for particulates to verify that there is no unacceptable release of particulate matter when in contact with body fluid. Devices tested had net particle concentrations lower than the acceptance criteria for both particles greater than 2 µm and 5 µm.</p>
<p><u>Interconnect Flexural Stress Test:</u> Samples mechanically identical in form to the device were attached to silicone eye models to simulate the actual implanted condition. These assemblies were affixed to a fixture that imparted an oscillating deflection that simulated the maximum accelerations that would be experienced by the device implanted in the eye. The test was run for 5 years equivalent lifetime to verify the robustness of the interconnection between the coil, array and package. Test assemblies were measured for resistance and leakage current to solution. The test samples met established acceptance criteria.</p>
<p><u>Device Lifetime – Active Soak Test:</u> Implants were stimulated while soaking under accelerated aging conditions and evaluated for functional performance. The testing found that the implant operated as intended over the specified life of the device. No signs of corrosion on the package, braze or coil were observed.</p>
<b>Implant (Packaged &amp; Sterilized)</b>
<p><u>Biocompatibility:</u> Biological testing was performed on the implantable components in accordance with ISO 10993-1. Testing included cytotoxicity, irritation, sensitization, acute systemic toxicity, pyrogenicity, subchronic toxicity, genotoxicity and implantation. The implantable components passed these biological tests. The implantable components were also evaluated for biocompatibility in terms of carcinogenicity and chronic toxicity without the need for further testing per ISO 10993-1 and FDA G95-1 Guidelines. The testing and evaluation established that the implantable components were suitable for long-term implantation.</p>
<p><u>Sterility:</u> The implantable components are sterilized with ethylene oxide. The sterilization process has been validated according to ANSI/AAMI/ISO 11135:1994 and EN 556 requirements for terminally-sterilized medical devices. The Second Sight Argus II product family has been accepted into the validated processing group through an adoption study. Ethylene oxide (EtO) residual testing has demonstrated that the sterilization process will not leave residual toxin levels inappropriate for use in the eye.</p>

### **Implant (Packaged & Sterilized)**

Dynamic Lifetime Test: Testing was performed on implants using a test model system simulating the stresses of saccadic micro-motion. During testing, the implants were powered under the maximum anticipated use conditions. The on-going study is being performed under real time conditions in the presence of saline. At the time of the most recently collected data (424 days and 53 days for right and left eye implants, respectively), the implant is meeting specification. A minimum of 5 years real time data is to be collected.

Shipping, Packaging and Shelf-Life Evaluation: A series of tests were conducted to validate the sterile packaging in compliance with ISO 11607-1:2006. The testing (stability testing, microbial challenge and bubble test) demonstrated the long-term integrity of the packaging and verified that the packaged components (i.e., the implant and tack) can safely withstand the stresses associated with shipping.

### **BENCH TESTING FOR THE EXTERNALS SUBSYSTEM AND THE FITTING SUBSYSTEM**

Bench testing has demonstrated the electrical safety and performance of the externals and fitting subsystems.

### **ELECTROMAGNETIC COMPATIBILITY**

The Externals System and fitting subsystem accessories met electromagnetic interference and electromagnetic compatibility requirements based on IEC 60601-1-2 and EN 300 330-1 for intentional and unintentional radiators. The tests demonstrated that the systems meet standards for radiated emissions from 30 to 1000 MHz, immunity from radiated fields ranging from 80 to 2700 MHz, immunity from electrostatic discharges up to 8 kV, RF common mode immunity and power frequency magnetic field immunity. All commercially available fitting system accessories indicate compliance to their applicable standards.

In addition to the electromagnetic compatibility testing described above, the Argus II System was evaluated for its electromagnetic compatibility with the following known emitters:

- Security and Logistical Systems (includes radio frequency identification systems, metal detectors, electronic article surveillance systems, and tag deactivators)
- Cellular phones and other personal communication devices
- Microwave ovens
- US Coast Guard transmitters

The Argus II System was also evaluated for its ability to safely coexist with other Argus II Systems.

In the presence of these possible sources of electromagnetic interference, the Argus II System continues to meet its essential performance requirements (as defined in IEC 60601-1-2) in that no unintended or unsafe stimulation is delivered.

### **BASIC SAFETY AND ESSENTIAL PERFORMANCE**

The externals and fitting subsystems met all applicable requirements for medical electrical equipment and systems according to IEC 60601-1. Tests included requirements on protection from electrical shock, protection from mechanical hazards, protection against excessive temperatures and other hazardous situations.

### **BIOCOMPATIBILITY**

The applicable patient contacting components were tested for cytotoxicity, sensitization, and irritation in accordance with of ISO 10993-1:2003. The components passed the testing and were determined to meet the biocompatibility requirements for their intended use.

### **RELIABILITY/ENVIRONMENTAL TESTING**

The Externals System passed all tests for operation at its minimum and maximum operating temperature, humidity and pressure. The Externals System also passed vibration testing in accordance with EN 60068-2-64 Test Fh.

### **SPECIFIC ABSORPTION RATE AND CURRENT DENSITIES**

The Externals System was analyzed and shown to be within applicable IEEE and ICNIRP safety standards on specific absorption rate and current densities.

### **PACKAGING**

Shipping and packaging integrity for all components of the Externals System and for the laptops and communication adapter of the fitting system passed the ISTA Test Procedure 2A. This testing included preconditioning for extremes in atmospheric conditions.

### **FUNCTIONAL**

The externals and fitting subsystems passed a wide range of functional testing to internal requirements covering all aspects of device and system usage.

### **ANIMAL STUDIES**

Objectives. The objectives of the chronic animal testing were to aid the development of the Argus II implant and to verify the design intended for clinical use. The majority of this testing was performed with mechanical models (i.e. non-active devices) of the Argus II implant to evaluate the mechanical design of the implant and the surgical implantation

technique. The remainder of the testing was performed with partially or fully active implants, to test the functionality of the device.

*In vivo* animal testing was performed in healthy canines. The studies typically lasted for a period of 3 to 6 months, or until a serious adverse event occurred (e.g. retinal detachment or unresolved infection). Summaries of the animal studies conducted during the design development and design verification process for the Argus II System are provided below.

## **MECHANICAL MODEL STUDIES**

- *Design Development Series:* A total of 30 canines were implanted with various mechanical models of the Argus II during the design development process. During the design development process, the design and surgical implantation technique were iterated many times to address feedback from surgeons and to incorporate changes intended to improve the clinical outcomes. Based on the results from these animals, a final design configuration was determined and was implanted in 3 canines.
- *Design Validation Series:*
  - A total of 3 canines were implanted with the design configuration of the Argus II used in the beginning of the human clinical trial. This study demonstrated the mechanical design was suitable and safe for use in humans.
  - Midway through the clinical trial, the implant design was modified to improve its safety and performance. This upgraded design was re-validated. An additional 6 canines were implanted with mechanical models representative of an upgraded design. The upgraded design proved to be surgically feasible to implant. No full thickness damage of the retina was observed and histological analysis showed general preservation of the retina in the area to be stimulated.

## **ACTIVE IMPLANT STUDIES**

- *Design Development Series:* Four canines were implanted with partial or fully active versions of the Argus II during the design development process to assess device functionality in animals.
- *Validation Study for Temperature Rise:* A temperature study conducted in canines verified that the outer surface temperature of the implant does not rise more than 2°C above the normal surrounding body temp of 37°C.
- *Validation Study for Device Functionality:*
  - Three canines were implanted with fully active Argus II devices to verify the functionality of the device following implantation. All three implants met the criterion of the primary endpoint: successful device functionality at 2 weeks post implant. This demonstrated that the device successfully survived surgical implantation. In addition to meeting their primary end point, two of the devices

maintained successful functionality for the duration of the 6 month study. The third device was explanted after the 3 month mark due to clinical issues with the canine. However, at the 3 month mark, the device was also functioning successfully.

- Following modification of the implant design midway through the clinical trial, validation was repeated in two additional canines utilizing devices that incorporated the upgraded implant design. The primary endpoint was unchanged from the previous study. At the 2 week post implant time point, the devices maintained their functionality. The study was continued for an additional two weeks with the devices continuing to function within specification.

## **EXPLANT STUDY**

A total of 3 healthy canines that had been implanted with mechanical models of the Argus II were selected to have their device explanted to evaluate and refine the explantation procedure. The study found that the device could be safely explanted.

## **X. SUMMARY OF CLINICAL INVESTIGATION**

### **OVERVIEW OF CLINICAL INVESTIGATION**

A prospective clinical trial was conducted to evaluate the safety and probable benefit of the Argus II Retinal Prosthesis System in providing visual function to blind subjects with severe to profound retinitis pigmentosa. This was a non-randomized, single-arm study. (due to the rarity of the patient population, a large, randomized clinical trial was not feasible). Subjects served as their own controls on all tests that were performed with the System both ON and OFF.

A total of 30 subjects were enrolled at 10 centers (6 in the United States and 4 in Europe). This study was conducted under an approved Investigational Device Exemption in the U.S. and appropriate approvals were obtained from the European Competent Authorities to conduct this study. In addition, Institutional Review Boards and Ethics Committees approved this study at each center and provided ongoing review of the study.

### **SUBJECT SELECTION CRITERIA**

The main criteria for enrollment in the trial were that a subject was required to:

- Have a confirmed history of retinitis pigmentosa [in the US] or outer retinal degeneration [in Europe] with bare light perception or worse vision in both eyes;
- Have functional ganglion cells and intact optic nerve (as documented by full-field flash detection or electrically evoked response);
- Have a confirmed history of useful form vision; and
- Be at least 25 years of age [in US and Switzerland] or at least 18 years of age [in France and UK].

The main reasons for exclusion from the study were if a subject had a disease or condition that would impede the ability to implant the device, or would prevent the System from functioning for the duration of the trial, or that prevented adequate visualization of the retina. Additional exclusion criteria were defined in the study protocol.

## **STUDY POPULATION**

Thirty (30) subjects were implanted with the Argus II Retinal Prosthesis System. Twenty-nine (29) were diagnosed with retinitis pigmentosa (one of whom had Leber's Congenital Amaurosis), and 1 with choroideremia. At baseline, all subjects were functionally blind and had bare light perception or worse in both eyes, defined as residual vision worse than 2.9 logMAR, and the ability to reliably detect at least a full-field flash ( $n = 29$ ) or have an electrically evoked response ( $n=1$ ). Most subjects' vision had declined to bare light perception in their mid-30's (median 38 years, range 20-69). By the time subjects were implanted with the Argus II device, they had been at bare light perception for many years (median 17.5 years, range 1.5-25 years). As such, most were well-adapted to being blind.

Of the thirty subjects recruited in the study, 21 were male and 9 female. The median age at time of implant was around 58 years, and with the exception of one 27 year old subject, all subjects were between 45 and 77 years.

## **STUDY PERIOD**

Enrollment in the study took place between June 6, 2007 and August 11, 2009. As of March 15, 2012, all subjects had been implanted for a minimum of 2.5 years (with the exception of one subject explanted at 1.2 years). The average length of follow-up was 3.5 years (range 2.6 – 4.8 years).

## **ADVERSE REACTIONS AND COMPLICATIONS**

Throughout the trial, subjects were actively monitored for adverse events at the regular clinical visits and asked to visit the site at any time should they experience signs or symptoms of adverse events between visits. Adverse events were reviewed and adjudicated by an Independent Medical Safety Monitor who adjudicated each event as to its relatedness (i.e. whether it was primarily device-, surgery-, or subject-related) and whether or not it met the regulatory definition of a serious adverse event (SAE).

## **DEFINITION OF ADVERSE EVENTS**

In the study, serious adverse events (SAEs) were medical occurrences that:

- Necessitated medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure; or
- Caused permanent impairment of a body function or permanent damage to body structure; or
- Required hospitalization or prolonged hospitalization.

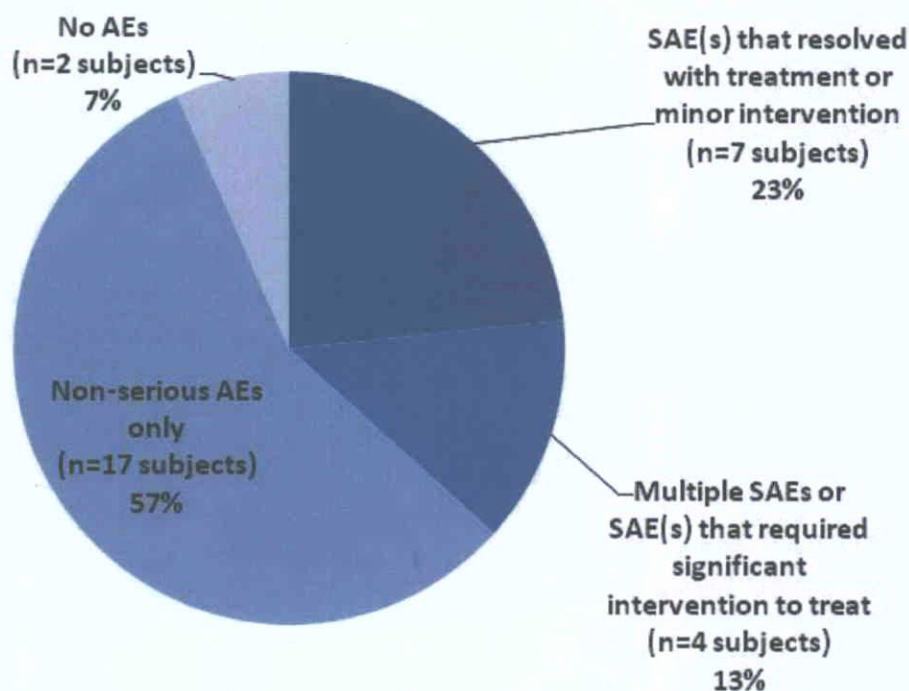
Events not meeting the above criteria were considered non-serious. All device- or surgery-related events are summarized below.

## **OVERVIEW OF SAFETY EXPERIENCE**

Nineteen subjects (63%) experienced no, or only non-serious, adverse events. These non-serious events were treated routinely with medication or observation only. An additional 7 subjects experienced SAEs that resolved with topical medication or minor interventions.

The remaining 4 subjects were distinct from the other subjects in that they had a higher rate of adverse events due to a cascade of related events. In total, these 4 subjects accounted for 57% of all serious adverse events (SAEs) and 24% of all non-serious adverse events. Refer to Figure 3.

**FIGURE 3: OVERVIEW OF SAFETY EXPERIENCE  
(N=30 SUBJECTS)**



#### Serious Adverse Events

During the study, nineteen subjects did not have any device- or surgery-related SAEs. Eleven subjects experienced a total of 23 device- or surgery-related SAEs (Refer to Table 3). Ten of the 23 events were considered to be related to the Argus II device and the remaining 13 were considered to be related to a surgical procedure.

One subject's device was explanted at 1.2 years due to recurrent conjunctival erosion and refractory hypotony. There were no other explants during the study.

Certain trends were observed in the SAEs. First, the majority of SAEs occurred within the first few months post-implant (more than 60% occurred within the first 6 months and 35% occurred within the first 6 weeks). Second, SAEs tended to cluster in a few subjects. Two subjects accounted for almost half of all SAEs (10/23). In these cases, the main event either required multiple interventions to treat it or the subject experienced a cascade of inter-related events.

**TABLE 3: SERIOUS ADVERSE EVENTS (DEVICE- OR SURGERY-RELATED)**

Reportable Term - Serious	# of Subjects	# of Events	% Subjects (n=30)
Conjunctival dehiscence	3	3	10.0%
Conjunctival erosion	3	4	10.0%
Corneal Melt - infective	1	1	3.3%



Corneal Opacity	1	1	3.3%
Fibrotic events:	3	3	10.0%
<i>RD – rhegmatogenous</i>	<i>1</i>	<i>1</i>	<i>3.3%</i>
<i>RD - tractional and serous</i>	<i>1</i>	<i>1</i>	<i>3.3%</i>
<i>Retinal Tear</i>	<i>1</i>	<i>1</i>	<i>3.3%</i>
Hypotony	4	4	13.3%
Intraocular inflammatory events:	3	4	10.0%
<i>Endophthalmitis - infective</i>	<i>3</i>	<i>3</i>	<i>10.0%</i>
<i>Uveitis</i>	<i>1</i>	<i>1</i>	<i>3.3%</i>
Keratitis - infective	1	1	3.3%
Re-tack	2	2	6.7%
Uveitis	1	1	3.3%

### Non-Serious Adverse Events

Any adverse event that did not meet the definition of an SAE was considered to be a non-serious adverse event. These events normally resolved without treatment or were treated with medical management (i.e. they did not require surgical intervention). There were 140 non-serious device-or surgery-related adverse events (in 28 subjects), of which 78 were device-related and the remaining 62 were surgery-related. The following non-serious events were reported (number of events is indicated in parentheses): ocular pain (17), conjunctival congestion (11), epiretinal membrane (11), elective revision surgery (7), non-serious hypotony (7), suture irritation (7), choroidal detachment (6), uveitis (6), inflammatory conjunctivitis (5), retinal thickening with cystoid macular edema (CME) (5), ocular inflammation (4), retinal thickening with no cystic changes (4), vitreous hemorrhage (4), headache (3), high intraocular pressure (3), hyphema (3), keratic precipitates (3), corneal vascularization (2), epiphora (lacrimation) (2), and foreign body sensation (2). There was one reported case of each of the following events: 360° circumferential vitreous band traction, choroidal effusion, conjunctival cyst, conjunctival dehiscence, conjunctival erosion, corneal abrasion, corneal dryness, corneal epithelial defect, corneal filaments, corneal fold, corneal suture broken, decrease in light perception, fibrosis around the tack, filamentary keratitis, nausea, nystagmus increase, ocular fibrin, proliferative vitreo-retinopathy, ptosis, serous retinal detachment, tractional retinal detachment, retinal folds, retinoschisis, rubeosis, scleral patch displacement, scleritis, sub-conjunctival eyelashes, and vertigo..

### Surgical Re-Interventions

Nine subjects required a surgical re-intervention(s) to treat a device- or surgery-related adverse event(s). Seven subjects had elective revision surgery. Refer to Table 4.

In cases where it was necessary to remove all or part of the implant and/or tack (i.e. 1 case of explant and 3 cases where the retinal tack was removed to reposition the implant during an elective revision surgery), no adverse sequelae occurred.

**TABLE 4: SURGICAL RE-INTERVENTIONS**

	# of Subjects	# of Events	% Subjects (n=30)
Re-intervention to treat an AE:	9		26.7%
<i>Conjunctiva repair</i>	5	12	16.7%
<i>Corneal scraping with EDTA</i>	1	1	3.3%
<i>Device explant</i>	1	1	3.3%
<i>RD repair</i>	2	4	6.7%
<i>Re-tack</i>	2	2	6.7%
<i>Treatment of hypotony</i>	2	4	6.7%
<i>Laser - Retinal tear</i>	2	3	6.7%
<i>Cross linking for corneal melt</i>	1	1	3.3%
Elective revision surgery	7	7	23.3%

RD = retinal detachment

EDTA = Ethylenediaminetetraacetic acid

**Implant Failures**

One Argus II Implant experienced an intermittent communication link beginning at 10 months post-implant which led to a significant decline in the functionality of the device. This device eventually failed approximately 4 years post-implant; however, the device remained implanted.

**SOURCES OF POTENTIAL BIAS IN THE ARGUS II CLINICAL TRIAL****PROTOCOL DEVIATIONS**

Protocol compliance was monitored throughout the study and protocol deviations were recorded and evaluated for their potential effect on study outcomes. Approximately 25% of deviations were due to a single exam or a follow-up visit being performed out of window (i.e. a few days/weeks early or late). Approximately 25% of deviations were due to minor modification made to a test method or test schedule in advance of a formal protocol amendment. Fifteen percent (15%) were due to an exam not being performed in the fellow eye (e.g., eye exam or fluorescein angiography). Fifteen percent (15%) were for a test not being performed due to equipment malfunction or a medical reason (e.g., OCT not possible due to lack of view into the eye). The remaining 20% of deviations were due to a test or exam not being completely (or correctly) performed. In summary, these protocol deviations which occurred during the study did not significantly affect the evaluation of the safety and probable benefit of the Argus II System.

**INVESTIGATOR BIAS**

The potential for investigator bias in the study was limited in several ways. A total of 10 sites participated in the study. Each site enrolled between 1 to 7 subjects, with the average being 3 subjects per site. Therefore, no investigator contributed more than 25% of the subjects in the study.

The practice of vitreoretinal surgery and ophthalmic follow-up is consistent throughout the US and Europe, where the study was conducted. All principle investigators, and, if different, all retinal surgeons, were chosen following the same selection criteria. All were of internationally recognized competence and underwent the same training and study preparations. *None of the investigators responsible for the assessment of clinical adverse events and outcomes had financial conflicts of interest.*

Together, these measures limited the potential for investigator bias in the study.

## **REGIONAL BIAS**

This study was conducted in the US and Europe. Fourteen subjects were enrolled in the US and 16 were enrolled in Europe. The study was analyzed to ensure that the data collected from centers outside the US were valid and to demonstrate that the ethical aspects, methods used during the study, the practice of ophthalmology, and the quality of the investigators was comparable for the US and European sites. Also, the prevalence of Retinitis Pigmentosa was shown to be similar in both regions. In addition, an analysis of the demographics of the subjects revealed that those enrolled in the Europe were comparable to those enrolled in the US. This analysis demonstrated that there were no significant regional differences that could have affected the outcomes in the study.

## **GENDER BIAS**

The subgroup analysis stratified by gender demonstrated that the outcomes with the Argus II System were comparable for men and women and that neither group performed substantially better or worse than the other on any of main outcomes in the study. There were only 9 women enrolled in the study; therefore, some observed minor differences may have been due to the small sample size of women. Based on this analysis, there is no evidence of a gender effect or difference in outcomes with the Argus II System between men and women.

## **XI. RISK PROBABLE BENEFIT ANALYSIS**

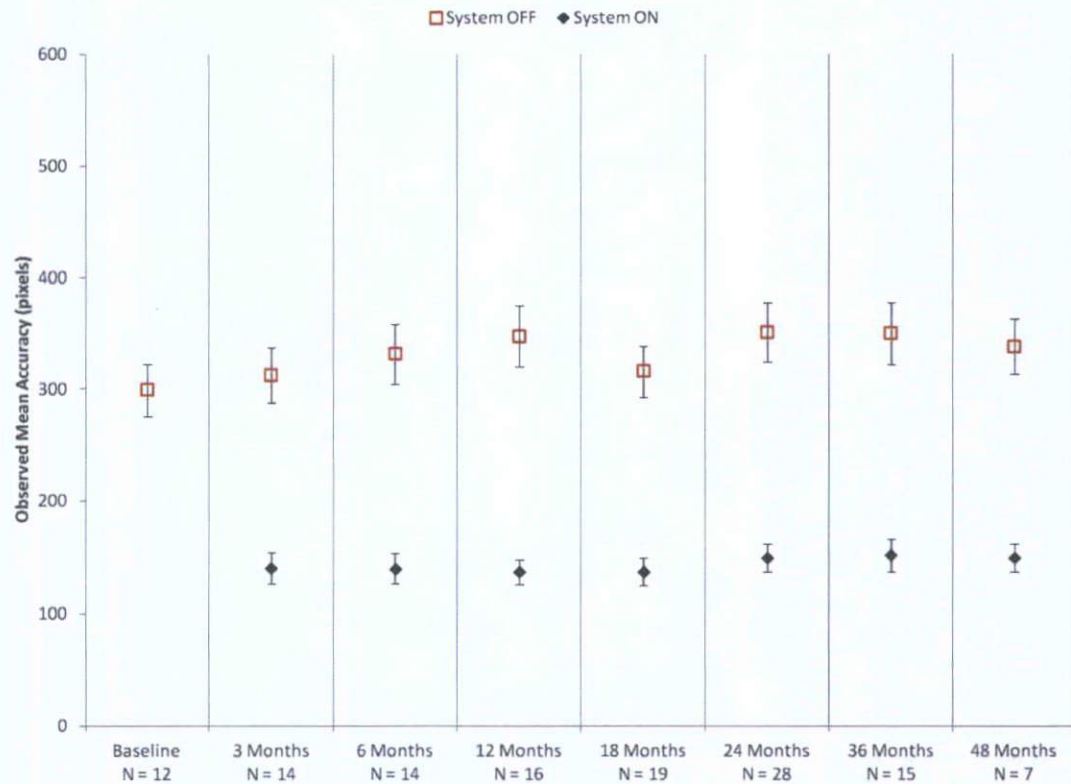
The Argus II System provided all 30 subjects with benefit as measured by visual function tests, although this level of benefit was variable. All 30 subjects were able to see visual percepts when the Argus II was electrically activated.

On the Square Localization test (i.e., object localization), subjects were consistently able to perform better with the System ON versus System OFF over the course of the study. Figure 4 displays the observed mean accuracy which indicates the subjects' mean distance from the center of the target square. Error bars represent the mean of the standard error.

On the Direction of Motion test, subjects were consistently able to perform better with the System ON versus System OFF over the course of the study. Figure 2 displays the observed mean accuracy which indicates the mean response error between the angle displayed and the subject's response. Error bars represent the mean of the standard error.

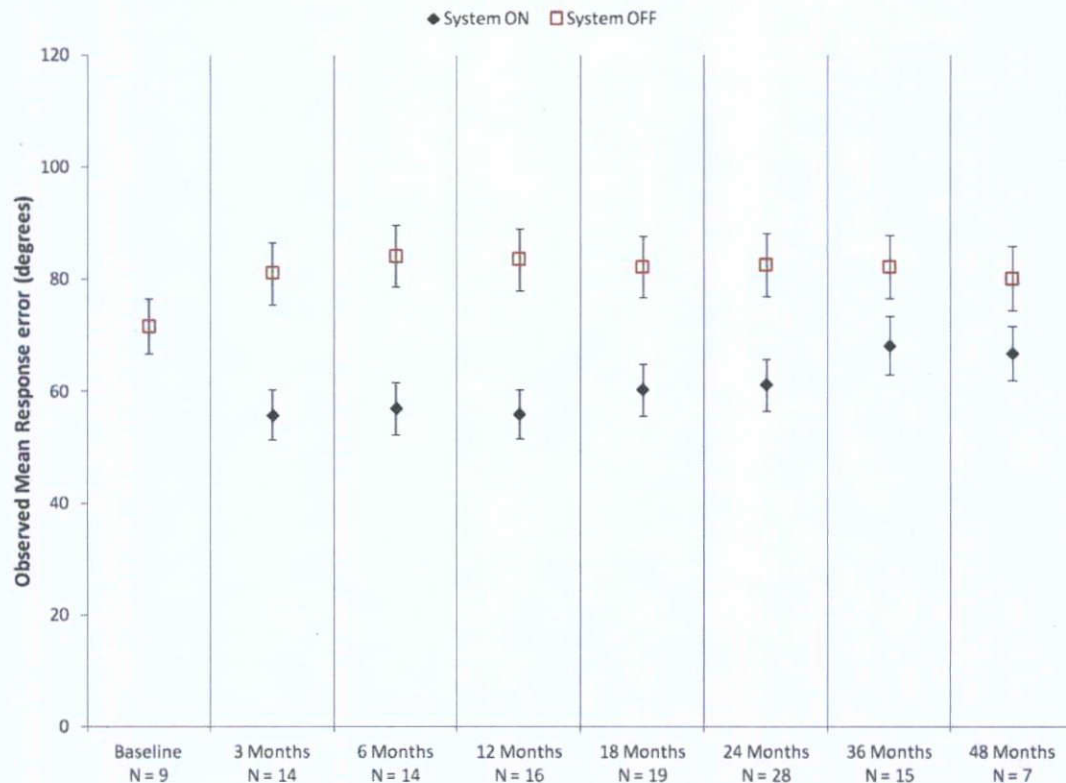
On the Grating Visual Acuity test, the most difficult of the 3 tests, 27% of subjects were able to reliably score on the scale (between 1.6 and 2.9 logMAR with a confidence interval within the scale) at least once with the System ON, while none of the Argus II subjects were able to score on the scale with the System OFF in either eye (Refer to Table 5).

**FIGURE 4: SQUARE LOCALIZATION (OBSERVED MEAN ACCURACY)**



NOTE: Since this test was introduced midway through the study, the Baseline to 12-month results were only from subjects enrolled in 2009. Subjects enrolled in the study in 2007 and 2008 first performed this test at either their 18- or 24-month follow-up visit.

**FIGURE 5: DIRECTION OF MOTION (OBSERVED MEAN RESPONSE ERROR)**



**NOTE:** Since this test was introduced midway through the study, the Baseline to 12 month results were only from subjects enrolled in 2009. Subjects enrolled in the study in 2007 and 2008 first performed this test at either their 18 or 24 month follow-up visit.

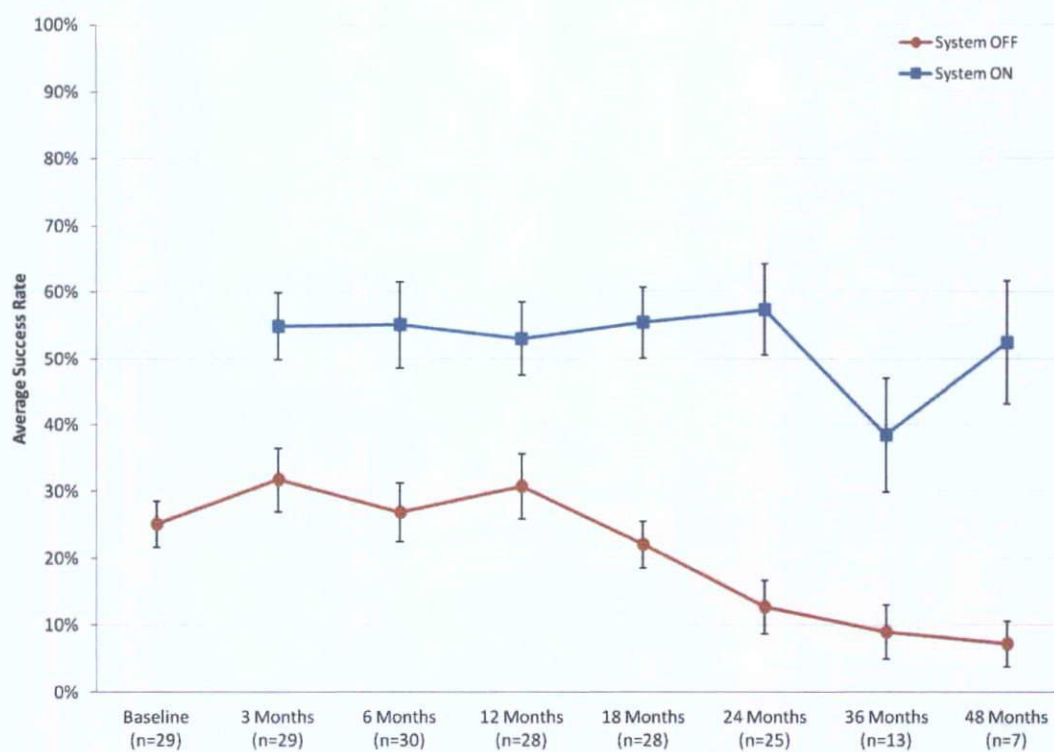
**TABLE 5: GRATING VISUAL ACUITY**

	% (n) of Subjects Whose Visual Acuity Improved to >2.9 LogMAR*
System ON	27% (8)
System OFF Implanted Eye	0% (0)
System OFF Fellow Eye	0% (0)

\* Best result at any follow-up visit.

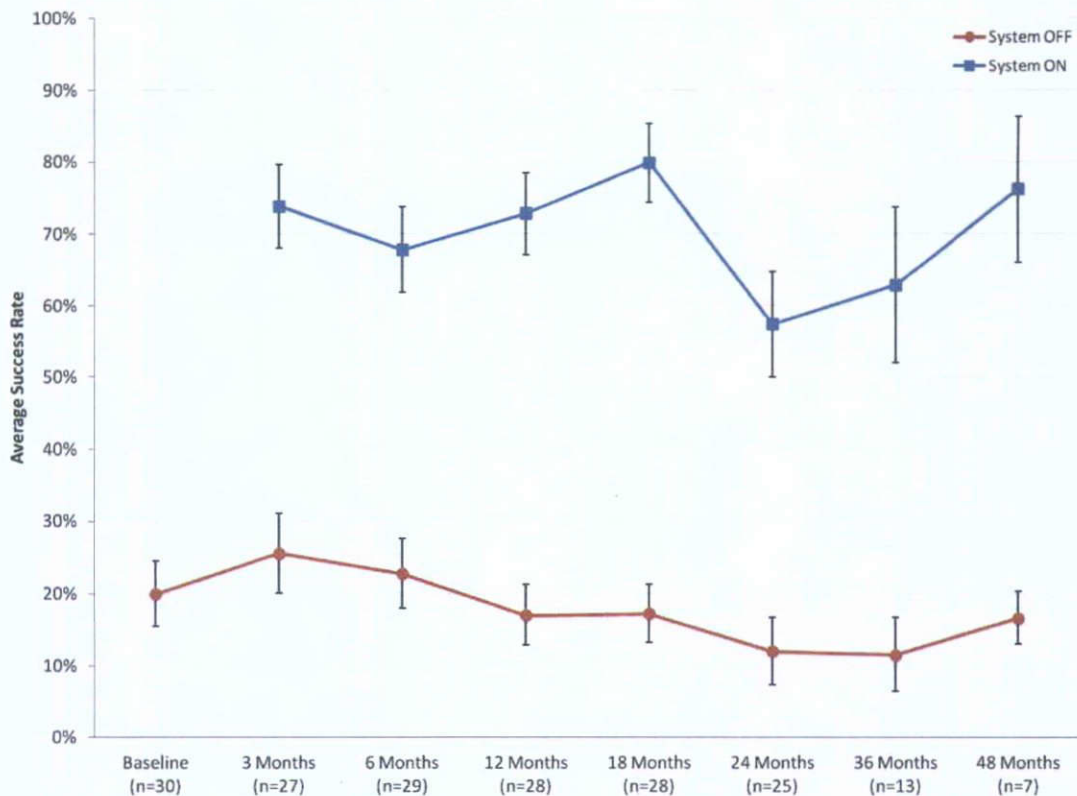
The Argus II System was also able to provide subjects with benefit as measured by objectively-scored, partially-controlled functional vision tests. Subjects consistently performed better with the Argus II System ON vs. OFF on orientation and mobility tests (finding a door and following a line, Figure 6 and Figure 7, respectively).

**FIGURE 6: DOOR TASK AVERAGE SUCCESS RATES (OBSERVED MEANS)**





**FIGURE 7: LINE TASK AVERAGE SUCCESS RATES (OBSERVED MEANS)**



Self-report questionnaires of activities of daily living and quality of life indicated mild improvement (Massof Activity Inventory) or no change (VisQOL), respectively.

An assessment of Argus II subjects in and around their home by independent, certified low vision rehabilitation specialists was also performed. This assessment, called the Functional Low-vision Observer Rated Assessment (FLORA) was designed to evaluate how the Argus II System affected subjects' well-being and functional vision. It was added to the study in 2010 at which time subjects' length of follow-up ranged from 1.4 to 3.7 years post-implant.

In no cases did the assessors report that the Argus II System had a negative impact on subjects. In 77% of cases, assessors using the FLORA determined that the subject was receiving (or had received at one time) functional vision and/or well-being benefit from the Argus II System. Refer to Table 5.



**TABLE 6: SUMMARY OF FLORA RESULTS (N=26 SUBJECTS)**

<b>Positive effect n (%)</b>	<b>Mild positive effect n (%)</b>	<b>Prior positive effect n (%)</b>	<b>Neutral effect n (%)</b>	<b>Negative effect n (%)</b>
9 (35%)	7 (27%)	4 (15%)	6 (23%)	0 (0%)

<b>Positive Effect</b>	<b>No positive effect</b>
20 (77%)	6 (23%)

Note: 4 subjects did not participate in the FLORA.

## CONCLUSIONS DRAWN FROM THE STUDIES

Pre-clinical in vitro and in vivo testing demonstrated the Argus II Retinal Prosthesis System meets applicable international standards and Second Sight-defined design requirements. A 6 patient feasibility study with a first generation device (Argus 16) demonstrated that a retinal prosthesis could be implanted chronically in human subjects. Long-term data collected from this study demonstrated the safety and proof of concept that an electrode array could be used to stimulate the retina to elicit visual percepts in blind subjects. Data from the Argus 16 study provided important design input for the next generation implant (Argus II), external equipment, and stimulation fitting strategies.

A 30 subject prospective clinical trial was conducted which demonstrated that the Argus II System is safe and will provide a probable benefit to the indicated patient population. All subjects in the clinical trial had been implanted a minimum of 2.5 years follow-up data, with several subjects having over 4 years of follow-up data. The long-term safety results are acceptable, with the majority of events resolving with no or minimal intervention. Serious adverse events were clustered in a few subjects and most occurred within the first 6 months post-implant. Furthermore, based on a trend toward reduced adverse events as the trial progressed and more experience was gained with the device, it is likely that the safety profile of the Argus II System will continue to improve with increasing surgical experience with these devices. The risk, therefore, is acceptable, especially when considering that the adverse events are occurring in blind eyes, for which decreased vision is not a significant risk. The performance analysis showed that a majority of subjects using the Argus II System have improved visual function that ranged between subjects from light perception to at least hand motion, or counting fingers vision. Assessments of subjects in their normal environments by low vision therapists also demonstrated that the majority of subjects received positive effects from the Argus II System in terms of well being and/or functional vision. These results represent a significant improvement and benefit for these subjects, especially when considering that they have no other approved treatment options for their irreversible degenerative disease.

When considering all the data, it has been demonstrated that the Argus II System poses an acceptable risk to people with severe to profound retinitis pigmentosa in exchange for a probable benefit – that of improvements in visual function, functional vision, and/or well-being.

## **XII. PANEL RECOMMENDATION**

At an advisory meeting held on September 28, 2012, the Ophthalmic Devices Panel of the Medical Devices Advisory Committee recommended that Second Sight Medical Product's HDE for the Argus® II Retinal Prosthesis System be approved.

## **XIII. CDRH DECISION**

CDRH has determined that, based on the data submitted in the HDE, that the Argus® II Retinal Prosthesis System will not expose patients to an unreasonable or significant risk or illness or injury, and the probable benefit to health from using the device outweighs the risks of illness or injury, and issued an approval order on February 13, 2013.

## **XIV. APPROVAL SPECIFICATIONS**

Directions for use: See the Physician's Labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See Approval Order.

## **XV. REFERENCES**

*General Program Memorandum #G91-1: Device Labeling Guidance.*  
<http://www.fda.gov/cdrh/g91-1.html>

Issued: 12/11/01  
Revised: 3/10/05